



Wiadomości Lekarskie

Czasopismo Polskiego Towarzystwa Lekarskiego



Pamięci
dra Władysława
Biegańskiego

TOM LXXII, 2019, Nr 9 cz II, wrzesień

Rok założenia 1928

W ogłoszonym 31 lipca br. przez Ministra Nauki i Szkolnictwa Wyższego wykazie czasopism naukowych Wiadomości Lekarskie otrzymały 20 punktów (pozycja 27088).

Wiadomości Lekarskie is abstracted and indexed in: PubMed/Medline, EBSCO, SCOPUS, Index Copernicus, Polish Medical Library (GBL), Polish Ministry of Science and Higher Education.

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Zamówienia na prenumeratę przyjmuje Wydawnictwo Aluna:

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Prosimy o dokonywanie wpłat na numer rachunku Wydawnictwa:
Credit Agricole Bank Polska S. A.: 82 1940 1076 3010 7407 0000 0000

Cena prenumeraty dwunastu kolejnych numerów: 240 zł/rok (w tym VAT)

Cena prenumeraty zagranicznej: 120 euro/rok.
Cena pojedynczego numeru – 30 zł (w tym VAT) + koszt przesyłki.
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Publisher:

ALUNA Publishing

ul. Przesmyckiego 29, 05-510 Konstancin – Jeziorna

www.aluna.waw.pl www.wiadomoscilekarskie.pl

www.medlist.org

Distribution and Subscriptions:

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ORIGINAL ARTICLE
PRACA ORYGINALNA

QUALIMETRIC ANALYSIS OF PROTON PUMP INHIBITORS IN UKRAINE

Olha V. Makarenko, Malika M. Karimova, Alona M. Masheiko, Nataliia M. Onul

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ABSTRACT

Introduction: On the pharmaceutical market of Ukraine, there are six international non-proprietary names of proton pump inhibitors (PPIs) – Omeprazole, Pantoprazole, Lansoprazole, Rabeprazole, Esomeprazole, Dexlansoprazole, which differ in a number of pharmacokinetic and pharmacodynamic parameters, safety profile, range of dosage forms and their cost.

The aim: To investigate the competitiveness of proton pump inhibitors registered in Ukraine by comparing the parameters of their quality properties using the method of qualimetric analysis.

Materials and methods: Qualimetric analysis is based on the deductive-axiomatic approach, which allows quantifying the qualitative properties of drugs and determining the degree of competitiveness of each of them in the pharmaceutical market of Ukraine. The qualitative properties of PPIs in terms of consumer are efficacy, safety, convenience of use and cost. The subject of the study was 133 trademarks of PPIs registered in Ukraine.

Results: The highest qualimetric values were obtained by omeprazole ($K^q = 0.73$) and its S-isomer esomeprazole ($K^q = 0.66$). Pantoprazole was inferior to them to a certain extent ($K^q = 0.64$). Lansoprazole ($K^q = 0.53$), rabeprazole ($K^q = 0.50$) and dexlansoprazole ($K^q = 0.44$) had the lowest values of the quality indices.

Conclusions: According to the results of the study of the PPIs' competitiveness for parameters characterizing efficacy, safety, convenience of use and cost, assessed by qualimetric analysis, it has been established that the most completely and qualitatively satisfying consumer's needs are omeprazole and its S-isomer, esomeprazole.

KEY WORDS: Competitiveness, Proton pump inhibitors, Pharmaceutical market, Qualimetric analysis, Ukraine

Wiad Lek 2019, 72, 9 cz II, 1769-1773

INTRODUCTION

Proton pump inhibitors (PPIs) are "drugs of choice" for the treatment of acid-related gastrointestinal diseases such as benign peptic ulcer and duodenal ulcer, gastroesophageal reflux disease (GERD), Zollinger-Elison syndrome [1].

The pharmaceutical market of Ukraine currently offers six international nonproprietary PPIs: Omeprazole (A02BC01), Pantoprazole (A02BC02), Lansoprazole (A02BC03), Rabeprazole (A02BC04), Esomeprazole (A02BC05), Dexlansoprazole (A02BC06) [1].

The basis of the molecular structure of all PPIs is the heterocyclic core of benzimidazole, which causes a single mechanism of action and the same efficacy of PPIs in the treatment of the acid-related diseases of the gastrointestinal tract [2].

PPIs differ in the structure of radicals on pyridine and benzimidazole cycles, which causes some difference in the pharmacokinetic and pharmacodynamic properties of these drugs [3, 4]. The peculiarities of the pharmacokinetic and pharmacodynamic profiles of certain PPIs may affect the patient's compliance and, consequently, the effectiveness of PPIs.

Qualimetric analysis allows comparing the proton pump inhibitors for the pharmacokinetic and pharmacodynamic parameters, the safety profile, the range of available dosage forms and their cost [5, 6, 7, 8].

The basis of the qualimetric analysis is deductive-axiomatic approach, which allows quantifying the qualitative properties of drugs and determining the level of competitiveness of each of them in the pharmaceutical market [5, 6, 7, 8].

THE AIM

The objective of the paper is to investigate the competitiveness of proton pump inhibitors registered in Ukraine by comparing the parameters of their quality properties using the method of qualimetric analysis.

MATERIALS AND METHODS

The subject of the study is the 133 trade names of proton pump inhibitors registered in Ukraine – Omeprazole (28 TN), Pantoprazole (54 TN), Lansoprazole (5 TN), Rabeprazole (15 TN), Esomeprazole (29 TN) and Dexlansoprazole (2 TN) [1].

Since qualitative properties of drugs are constant objective parameters, the qualimetric analysis was carried out by the non-expert (also known as analytical) method. The qualimetric analysis included the following steps: 1) determining the property indicators characterizing the PPIs and creating a so-called «property tree» in the table

form; 2) calculating the values of the weight factors of the individual properties; 3) defining the values of absolute property indices including reference and acceptable values for property indices; 5) bringing the values of absolute property indices to one unit of measure (relative property indices); 6) defining the values of objects quality indices; 7) the ranking of PPIs [6, 8].

RESULTS

The qualitative properties of PPIs in terms of consumer are efficacy, safety, convenience of use and cost.

Indicators that characterize the *efficacy* of PPIs were the following pharmacokinetic and pharmacodynamic parameters, such as the absolute bioavailability, the median time to reach to $C_{\max}(t_{\max})$, 24-hour median intragastric pH , the mean percent duration of time with intragastric $pH > 4$ and the number of clinical indications approved in the instructions for the medical use of PPIs.

Indicators that characterize PPIs' *safety* were PPIs acid trapping, the number of adverse reactions that may occur at a frequency of $\geq 1\%$, the possibility of appointment in hepatic and renal insufficiency without dose adjustments, the possibility of use for children and elderly, the possibility of use for pregnant women and women during breastfeeding.

Indicators characterizing PPIs' *convenience of use* were the market availability of brand-name drugs, generics, OTC-drugs, registration of parenteral dosage forms and children's medical forms, the number of registered doses in Ukraine.

The average cost of the oral dose was chosen as an indicator that characterizes PPIs' cost.

The property weight factors were determined by the Delphi method with the participation of five experts and calculated according to the formula [8]:

$$G'_i = \frac{G''_i}{\sum_{i=1}^n G''_i}$$

Where G'_i – the property weight factor;

G''_i – the weight of the individual properties for 5-point scale;

$\sum G''_i$ – the total value of the weight of the individual properties.

It was established, that the most significant property weight factors of PPIs were 24-hour intragastric pH , the mean percent duration of time with intragastric $pH > 4$, the number of clinical indications and the possibility of use for children ($G'_i = 0.06$).

“Tree of properties” and the property weight factors of PPIs are provided in Table I.

The value of absolute property indices – efficacy, safety and convenience of use were determined by the documentary method with instructions for the drug's use. The value of the cost absolute property was determined by the calculation method. Quantitative assessment of the absolute property indices were carried out on a scale of absolute values [8].

To bring the values of absolute property indices to one unit of measurement and provide their comparability among themselves, the conversion of absolute indices into relative ones was carried out using the rationing operation [8]:

$$K_{ij} = \frac{Q_{ij} - q_i^{ref}}{q_i^{ref} - q_i^{rej}}$$

Where K_{ij} – the relative index value;

Q_{ij} – the absolute property index value;

q_i^{ref} – reference value of the absolute property index;

q_i^{rej} – acceptable value of the absolute property index.

The quality index (K^k) of PPIs was calculated as arithmetic average by the formula [6, 8]:

$$K^k = \sum_{i=1}^n K_{ij} G'_i$$

Where K^k – the quality index;

G'_i – the property weight factor;

K_{ij} – the relative index value;

n – the number of indicators of the object properties taken into account.

Table II presents the results of a qualitative analysis of PPIs.

Thus, it was found that omeprazole ($K^k = 0.73$) and esomeprazole ($K^k = 0.66$) had the highest qualimetric rating. Pantoprazole was inferior to them to a certain extent ($K^k = 0.64$).

Lansoprazole ($K^k = 0.53$), rabeprazole ($K^k = 0.50$) and dexlansoprazole ($K^k = 0.44$) had the lowest values of the quality indices.

DISCUSSION

This study was conducted to quantify the competitive advantages of IPPs.

The quality index is a complex parameter that represents the sum of intermediate indicators – the quality indices of efficacy, safety, convenience of use and cost.

Thus, it was found that the highest *quality index of efficacy*, had esomeprazole ($K^{k_{efficacy}} = 0.22$). This is due to the high bioavailability (89 %) of esomeprazole, the fast achievement of the peak concentration of the drug in the blood (1-2 hours), the high antisecretory effect (24-hour median intragastric pH is 4.8 ± 0.7) and the duration of $pH > 4$ in the stomach during 15.5 hours ($64.6\% \pm 15.2$).

Lansoprazole ($K^{k_{efficacy}} = 0.20$) is slightly inferior to esomeprazole in terms of the quality index of efficacy. The only competitive advantage of lansoprazole compared to esomeprazole is large quantity of the clinical indications for use (10 vs. 7). Unlike esomeprazole, lansoprazole is recommended for healing of active benign gastric ulcer and active duodenal ulcer, maintenance of healed duodenal ulcers in adults [13, 16].

Dexlansoprazole, the proton pump inhibitor of the last generation, ranks third in terms of the quality index of efficacy ($K^{k_{efficacy}} = 0.17$). Despite the competitive values of pharmacokinetic and pharmacodynamic parameters, dexlansoprazole has only three indications – healing of erosive esophagitis, maintenance of healed erosive esophagitis and treatment of symptomatic non-erosive gastroesophageal reflux disease [13, 20].

Table I. The property weight factors of PPIs

Property indicators	The weight of the criterion for 5-point scale (average value), G_i	The property weight factor, G'_i
Efficacy		
The absolute bioavailability, %	3,80	0,05
The median time (T_{max}) to peak plasma concentrations (C_{max}), h	3,40	0,05
24-hour median intragastric pH	4,40	0,06
Mean percent duration of time with intragastric pH > 4, %	4,80	0,06
Clinical indications, units.	4,80	0,06
Safety		
Acid trapping (pKa)	3,00	0,04
Number of most common adverse reactions in adults (incidence ≥ 1 %)	3,80	0,05
The possibility of use in liver failure	3,40	0,05
The possibility of use in renal failure	3,40	0,05
The possibility of use for children under 12 years	4,40	0,06
Possibility of use for elderly people without dose adjustment	2,60	0,03
Possibility of use for pregnant women	4,00	0,05
Possibility of use for women during breastfeeding	3,80	0,05
Convenience of use		
Registration of brand-name drugs in Ukraine	4,00	0,05
Registration of generics in Ukraine	3,60	0,05
Registration of OTC-drugs in Ukraine	4,00	0,05
Registration of parenteral dosage forms	3,60	0,05
Registration of children's medical forms	3,60	0,05
Number of registered doses, units.	3,00	0,04
Cost		
The average cost of the oral dose, UAH.	3,60	0,05
TOTAL	$\Sigma G_i = 75,00$	1,00

The lowest value of the quality index of efficacy was established for rabeprazole ($K^k_{\text{efficacy}} = 0.13$), which is due to the lack of competitive advantages of its pharmacodynamic and pharmacokinetic parameters compared to other IPPs.

Calculation results of the *quality index of safety* showed that omeprazole ($K^k_{\text{safety}} = 0.28$) and its S-isomer esomeprazole ($K^k_{\text{safety}} = 0.25$) were identified as the safest. These drugs, unlike other PPIs, are allowed during pregnancy [15–20].

The lowest value of the quality index of safety was found in rabeprazole ($K^k_{\text{safety}} = 0.16$). Due to low acid trapping ($pKa = 4.9$), rabeprazole has limited use in pediatric practice [12, 18]. The ability of rabeprazole to work in a wide range of pH enables it to inhibit proton pump of the immune system cells [3, 14], which causes a number of specific adverse reactions, in particular, Flu-like symptoms, infections and inflammation of the throat and lining of the nose [18].

It is necessary to mention that all PPIs may be prescribed for hepatic and renal insufficiency without dose adjustment [15–20].

According to the *quality index of convenience of use*, it has been found that the most fully satisfying the needs of consumers are drugs of omeprazole ($K^k_{\text{convenience}} = 0.24$) and pantoprazole ($K^k_{\text{convenience}} = 0.22$) registered in Ukraine. In particular, OTC-forms of these drugs are available for consumers.

It should be noted that in Ukraine there are very limited presented children's dosage forms of IPPs. Among the IPPs registered in Ukraine in the form of powder or granules for preparing oral suspensions, only omeprazole is available in one trade name of Indian production. In addition, a distinctive feature of the pharmaceutical market in Ukraine is non-availability of the brand-name drugs of omeprazole and lansoprazole.

Drugs of omeprazole ($K^k_{\text{cost}} = 0.05$) have a competitive advantage in terms of the *quality index of cost*, which is due to the low average cost of the oral dose. The drugs of lansoprazole, rabeprazole and pantoprazole follow ome-

Table II. Results of qualimetric analysis of proton pump inhibitors in Ukraine

Indicators of qualitative properties		Reference value, q_i^{ref}	Acceptable value, q_i^{rej}	INN					
				Omeprazole	Lansoprazole	Pantoprazole	Rabeprazole	Esomeprazole	Dexlansopra- zole
Efficacy									
The absolute bioavailability, %	absolute	90	50	60* [9, 15]	80-90 [9, 16]	77 [9, 17]	52 [9, 18]	89* [19]	Not found [11, 20]
	relative			0,25	0,75	0,68	0,05	0,98	0,75
The median time (T_{max}) to peak plasma concentrations (C_{max}), h	absolute	1	5	1.5 (1-2) [15]	1.75 (1.5-2) [16]	2.5 [9, 17]	3.5 (2-5) [9, 18]	1.5 (1-2) [19]	1.5 (1-2; 4-5) [11, 20]
	relative			0,88	0,81	0,63	0,38	0,88	0,88
Mean intragastric pH ±standard deviation over 24 h after multiple doses of PPIs for healthy volunteers	absolute	5.5	2.1	3.5±1.0 [10]	4.1±0.7 [10]	3.5±1.4 [10]	4.5±0.5 [10]	4.8±0.7 [10]	4.55 [20]
	relative			0,41	0,59	0,40	0,71	0,79	0,72
Mean percent duration of time with intragastric $pH > 4$ after multiple doses of PPIs %	absolute	79,8	28,2	48.7±20.5 [10]	55.1±14.4 [10]	53.6±19.8 [10]	57.7±14.2 [10]	64.6±15.2 [10]	71 [20]
	relative			0,40	0,52	0,49	0,57	0,71	0,83
Indications, units	absolute	10	3	10 [4, 15]	10 [4, 16]	7 [4, 17]	7 [4, 18]	7 [4, 19]	3 [4, 20]
	relative			1,00	1,00	0,57	0,57	0,57	0,00
The quality index of efficacy, $K^k_{efficacy}$				0,17	0,20	0,15	0,13	0,22	0,17
Safety									
Acid trapping (pKa)	absolute	3,0	5,0	4,13 [12]	4,01 [12]	3,96 [12]	4,9 [12]	4,13 [12, 21]	4,01 [12]
	relative			0,44	0,50	0,52	0,05	0,44	0,5
Number of most common adverse reactions in adults (incidence ≥ 1 %)	absolute	1	10	6 [15]	4 [16]	7 [17]	5 [18]	6 [19]	5 [20]
	relative			0,44	0,67	0,33	0,56	0,44	0,56
The possibility of use in liver failure without dose adjustment	absolute	Yes	No	Yes [15]	Yes [16]	Yes [17]	Yes [18]	Yes [19]	Yes [20]
	relative			1,00	1,00	1,00	1,00	1,00	1,00
The possibility of use in renal failure without dose adjustment	absolute	Yes	No	Yes [15]	Yes [16]	Yes [17]	Yes [18]	Yes [19]	Yes [20]
	relative			1,00	1,00	1,00	1,00	1,00	1,00
The possibility of use for children under 12 years	absolute	Yes	No	Yes [4, 15]	Yes [4, 16]	Yes [4, 17]	No [4, 18]	Yes [4, 19]	No [4, 20]
	relative			1,00	1,00	1,00	0,00	1,00	0,00
Possibility of use for elderly people without dose adjustment	absolute	Yes	No	Yes [15]	No [16]	Yes [17]	Yes [18]	Yes [19]	Yes [20]
	relative			1,00	0,00	1,00	1,00	1,00	0,00
Possibility of use for pregnant women	absolute	Yes	No	Yes [15]	No [16]	No [17]	No [18]	Risk/benefit [19]	No [20]
	relative			1,0	0,00	0,00	0,00	0,5	0,00
Possibility of use for women during breastfeeding	absolute	Yes	No	No [15]	No [16]	No [17]	No [18]	No [19]	No [20]
	relative			0,00	0,00	0,00	0,00	0,00	0,00
The quality index of safety, K^k_{safety}				0,28	0,21	0,23	0,16	0,25	0,18
Convenience of use									
Registration of brand-name drugs in Ukraine	absolute	Yes	No	No [1]	No [1]	Yes [1]	Yes [1]	Yes [1]	Yes [1]
	relative			0,0	0,0	1,0	1,0	1,0	1,0
Registration of generics in Ukraine	absolute	Yes	No	Yes [1]	Yes [1]	Yes [1]	Yes [1]	Yes [1]	No [1]
	relative			1,0	1,0	1,0	1,0	1,0	0,0
Registration of OTC-drugs in Ukraine	absolute	Yes	No	Yes [1]	No [1]	Yes [1]	No [1]	No [1]	No [1]
	relative			1,0	0,0	1,0	0,0	0,0	0,0
Registration of parenteral dosage forms in Ukraine	absolute	Yes	No	Yes [1]	No [1]	Yes [1]	Yes [1]	Yes [1]	No [1]
	relative			1,0	0,0	1,0	1,0	1,0	0,0
Registration of children's medical forms (suspension for oral use)	absolute	Yes	No	Yes [1]	No [1]	No [1]	No [1]	No [1]	No [1]
	relative			1,0	0,0	0,0	0,0	0,0	0,0
Number of registered doses, units.	absolute	3	1	3 [1]	2 [1]	2 [1]	2 [1]	2 [1]	2 [1]
	relative			1,0	0,5	0,5	0,5	0,5	0,5
The quality index of convenience of use, $K^k_{convenience}$				0,24	0,07	0,22	0,17	0,17	0,07
Cost									
The average cost of the oral dose, UAH.	absolute	2,00	20,00	20 mg - 2,15 [22]	30 mg - 4,07 [22]	20 mg - 6,16 [22]	20 mg - 5,44 [22]	20 mg - 13,09 [22]	30 mg - 13,99 [22]
	relative			0,99	0,89	0,77	0,81	0,25	0,33
The quality index of cost, K^k_{cost}				0,05	0,04	0,04	0,04	0,01	0,02
The quality index, K^k				0,73	0,53	0,64	0,50	0,66	0,44
Rank				1	4	3	5	2	6

Note: * – the absolute bioavailability of repeated doses.

prazole. Drugs of esomeprazole and dexlansoprazole have the highest average cost of the oral dose.

CONCLUSIONS

According to the results of the study of the PPIs' competitiveness for parameters characterizing efficacy, safety, convenience of use and cost, assessed by qualimetric analysis, it has been established that the most completely and qualitatively satisfying consumer's needs are omeprazole and its S-isomer, esomeprazole.

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Conflict of interest:

The Authors declare no conflict of interest.

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Received: 01.04.2019

Accepted: 23.08.2019